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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,069	04/10/2001	Marschall S. Runge	D6179CIP	8710

7590 03/11/2003

Benjamin Aaron Adler
ADLER & ASSOCIATES
8011 Candle Lane
Houston, TX 77071

EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,069	RUNGE ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 23, 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6-10* is/are allowed.

6)☒ Claim(s) *1,2 and 11-13* is/are rejected.

7)☒ Claim(s) *3-4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed December 23, 2002. Currently, claims 1-4, 6-13 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims, applicant's arguments and the terminal disclaimer.

4. It is noted that the marked up copy of Claim 11 does not match the clean copy of Claim 11. The marked up copy of Claim 11 recites steps c-d, however the clean copy properly recites a-b. Thus, in the interest of compact prosecution, the clean copy of the claims is presumed to be the official claims.

Maintained Rejections

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

It is noted that no IDS has been filed and applicants did not respond to the notice.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Corral-Debrinski et al (Mutation Research, Vol. 275, pages 169-180, 1992).

Corral-Debrinski et al. (herein referred to as Corral-Debrinski) teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease. Corral-Debrinski teaches sampling cardiac tissue and estimating mtDNA damage using PCR (page 172, col. 1-2)(limitations of Claim 2). Table 1 and Table 2 illustrate control and atherosclerotic heart disease characteristics respectively for mtDNA deletion. Figure 2 illustrates the mtDNA deletion vs. age for control hearts and chronic coronary atherosclerotic hearts. It is evident that mtDNA damage occurs at a higher percentage in coronary atherosclerotic hearts than in control hearts.

Response to Arguments

The response traverses the rejection. The response asserts that Corral-Debrinski does not teach a method of evaluating the atherosclerotic state of an individual. This argument has been thoroughly reviewed, but is not found persuasive because Corral-Debrinski teaches an association of mtDNA. Thus, provided the association between mtDNA damages and coronary atherosclerotic heart disease,

Corral-Debrinski teaches a method of evaluating the atherosclerotic state of an individual.

The response asserts that Corral-Debrinski teaches analyzing cardiac tissues from pathology samples and does not analyze the arteries and the blood (page 6 of response filed December 23, 2002). This argument has been reviewed but is not convincing because the claims are drawn to collecting any tissue. Tissue encompasses not only arteries and blood, but also cardiac tissue as taught by Corral-Debrinski. The teachings of Corral-Debrinski anticipates the claimed invention.

It is noted that the response provides substantial discussion regarding the ability to use alternative tissue in the method. The response asserts that "it has been well known in the art that the mitochondria of damaged hearts are abnormal." The response also explicitly states that "because Corral-Debrinski examined heart tissue from deceased individuals, no association can be made between the observed damages and the progression arteriosclerosis." The response appears to be asserting that the claim in not enabled for the full scope, namely using any tissue. As written, the claims are not limited to only arteries and blood, therefore, the instant rejection anticipates the claimed invention.

The response asserts that the PCR amplification of Corral-Debrinski was limited to the detection of mutations in the mtDNA of the heart tissue whereas Applicants' describes the measurement of oxidative damage in the mtDNA as well as mutations by treating the DNA with FAPY glycosylase prior to PCR to enable detection of 8-oxo-deoxyguanosine lesions. It is noted that this limitation is not part of the instantly claimed

invention and would require an additional search in the event that such limitation were added to the claims.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) or Corral-

Debrinski et al (Mutation Research, Vol. 275, pages 169-180, 1992) and further in view of Herrnstadt et al. (US Pat. 6,218,117, April 2001).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay (limitations of Claim 2). Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold higher than that of human aortic samples without evidence of atherosclerosis (limitations of Claim 1, 2, 5). The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8, 10). Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

Corral-Debrinski et al. (herein referred to as Corral-Debrinski) teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease. Corral-Debrinski teaches sampling cardiac tissue and estimating mtDNA damage using PCR (page 172, col. 1-2)(limitations of Claim 2). Table 1 and Table 2 illustrate control and atherosclerotic heart disease characteristics respectively for mtDNA deletion. Figure 2 illustrates the mtDNA deletion vs. age for control hearts and chronic coronary

atherosclerotic hearts. It is evident that mtDNA damage occurs at a higher percentage in coronary atherosclerotic hearts than in control hearts.

Neither Yan nor Corral-Debrinski teaches methods of determining the efficacy of a drug by administering a drug to a sample and determining the level of mitochondrial DNA damage.

However, Herrnstadt teaches methods for identifying agents for treating a disease associated with altered mitochondrial function. Herrnstadt teaches that biological samples may be treated by heating in water to lyse cells contained in the sample and then extracting cellular DNA from lysed cells using an aqueous DNA extraction procedure. Specifically, Herrnstadt teaches that methods of comparing the ratio from a sample obtained before contacting a biological source with a candidate agent obtained after contacting the biological source with the agent.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of detecting atherosclerotic state of an individual by determining mtDNA damage with the improved method of determining whether drugs are efficient in reducing the risk of atherosclerosis in an individual. The art clearly provides that mtDNA damage is associated with atherosclerosis, see Yan and Corral-Debrinski. Therefore, once this is known in the art, the ordinary artisan would be motivated to determine possible treatments for such risks. Thus, the ordinary artisan would look to other methods of determining whether an agent is effective for reducing risk given the teachings in the art. Herrnstadt teaches that agents may be determined by comparing the mitochondrial DNA prior and following treatment. Therefore, the

ordinary artisan would have been motivated to have evaluated candidate agents, drugs, for the efficacy in treating a well known problem.

Response to Arguments

The response traverses the rejection. The response asserts that Herrnstadt teaches "only the quantification of the relative amounts of extramitochondrial and mitochondiral DNA in a sample and does not teach or suggest the measurement of the amount of mitochondrial DNA damage in a sample to assess the risk of atherosclerosis in an individual." This argument has been reviewed but is not convincing because Herrnstadt is relied upon for the teachings that comparing the ratio from a sample obtained before contacting a biological source with a candidate agent obtained after contacting the biological source with the agent.

The response asserts that there is no motivation to combine the teachings of Herrnstadt with Yan or Corral-Debrinski. This argument has been thoroughly reviewed, but is not found persuasive because the art teaches that mtDNA damage is associated with arteriosclerosis, see Yan and Corral-Debrinski. Therefore, the ordinary artisan would be motivated to determine possible treatments for such risks.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

9. Claims 1-2, 11-13 are rejected. Claims 3-4 are objected to as dependent upon a rejected claim. Claims 6-10 are allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Ferrari (J. of Cardiovascular Pharmacology, Vol. 28, Suppl. 1, pages S1-S10, 1996). Ferrari teaches mitochondrial DNA deletion rose to a maximum of 0.007% in normal hearts and increased to between 0.02% and 0.85% in CAD patients.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
February 26, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600